122,721 alone had fewer vomiting episodes (mean, two versus seven) \((P = .007)\). Six (86%) of the seven patients who received one dose of CP-122,721 alone as prophylaxis reported no delayed emesis. Acute emesis and delayed emesis were similar among the CP-122,721 doses. No adverse effects of CP-122,721 occurred.

This trial reports the first use of a substance-P antagonist to prevent cisplatin-induced emesis. The most dramatic finding was the prevention of delayed vomiting in 83% of the patients given a single prophylactic dose of CP-122,721. Only 17% of previously treated individuals had no delayed emesis in their prior course \((P = .006)\). This observation that NK\(_1\) receptor blockade prevents delayed emesis suggests that substance P may, in part, mediate this reflex. In patients receiving CP-122,721 alone as prophylaxis for acute cisplatin-induced emesis, vomiting was lessened compared with historical data \((7)\), showing activity against acute emesis. For patients who had experienced acute emesis with a serotonin antagonist and dexamethasone in prior cycles, control during a subsequent cycle with CP-122,721 did not decline as expected \((12)\). These data suggest that NK\(_1\) antagonists may provide additive acute control. Further study of NK\(_1\) receptor antagonists provides a singular opportunity to improve our understanding and control of emesis.

**References**


**Notes**

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M. G. Kris is a consultant to Pfizer, Inc., makers of CP-122,721, as well as to other pharmaceutical manufacturers; B. A. Pizzo holds stock in Pfizer, Inc.; and P. J. Hesketh has served as a consultant to Pfizer, Inc.

**An Explanation for the Increasing Incidence of Testis Cancer: Decreasing Age at First Full-Term Pregnancy**

For unknown reasons, the incidence of cancer of the testis has increased substantially among white male populations of several European countries, the United States, Australia, and New Zealand \((1)\). In Japan, the rates of testicular cancer have increased recently as well \((2)\). An increase in the rate in white populations was first noted among men born after 1920, but this increase was not consistently sustained for men born between 1930 and 1945 \((1)\). However, for men born in the 1950s onward, the increase in incidence has been uninterrupted. Explanations for this secular increase have been elusive. To some investigators, reports of a concomitant decrease in sperm counts in young men have suggested that an environmental exposure (e.g., pesticides and plant phytostrogens) might be responsible \((3)\).

A substantial body of experimental and epidemiologic evidence indicates that prenatal events or exposures are important risk factors for testis cancer \((4)\). Excess maternal nausea and vomiting in the prenatal period, prenatal exogenous exposure to diethylstilbesterol (DES), and maternal obesity have been associated with increased risk of testis cancer and with the risk of cryptorchidism, which is by far the strongest known risk factor for testis cancer \((5, 7)\). These shared risk factors have suggested that in utero estrogen exposure might be a common cause of both cryptorchidism and cancer of the testis. Animal experiments have shown that estrogen treatment of pregnant mice can lead to undescended and hypogenetic testis \((5)\). Similar abnormalities have been reported in male offspring of women exposed to DES and oral contraceptives during pregnancy \((6)\).

The risk of testis cancer associated with excess nausea and vomiting is greatest for nausea requiring medical treatment \((5)\). The strongest risk factors for such hyperemesis gravidarum are earlier age at pregnancy, nulliparity, and high body weight \((8)\). Increased levels of bioavailable estradiol are found in the
cer increase steadily, with a peak be-

through 1994. The AAIRs for testis can-

in Los Angeles County from 1972

and age-adjusted incidence rates

women. Table 1 provides age-specific

incidence among the corresponding

nation for the increase in testis cancer

continuous decline in maternal age at

again (10)

born in 1940. It has since risen once

nadir of less than 22 years for women

but it fell more or less continuously to a

United States, the mean age at FFTP

European women during the first half of

larly among men born since the 1950s,

ing incidence of testis cancer, particu-

(10)

compared with her second pregnancy

mester of a woman’s first pregnancy

with hyperemesis gravidarum compared

first trimester of pregnancy (FFTP) experienced by North

and decreasing age at first full-term

pregnancy (FFTP) experienced by North

American and presumably Western

women during the first half of this centu-

ry (10) is striking. In the United States, the mean age at FFTP

was 25.5 years for women born in 1910,

but it fell more or less continuously to a

nadir of less than 22 years for women

born in 1940. It has since risen once

again (10).

We propose that the three decades of

continuous decline in maternal age at

FFTP provides at least a partial expla-

nation for the increase in testis cancer

incidence among the corresponding

male offspring birth cohorts of these

women. Table 1 provides age-specific

and age-adjusted incidence rates

(AAIRs) of testis cancer for white males

in Los Angeles County from 1972

through 1994. The AAIRs for testis

cancer increase steadily, with a peak be-

between 1987 and 1989 that is more than
double the rate of the early 1970s, but

subsequently decline by about 15% in

the first half of the 1990s. Women who

were born between 1910 and 1940 and

experiencing a declining age at FFTP

would have male offspring born ap-

proximately between 1930 and 1960

(10). These sons would be entering their

peak ages (25-35 years) for testis cancer

risk in the 1950s. By the early 1990s,

men in the peak incidence ages for testis

cancer would increasingly be those

whose mothers sustained their FFTP af-

ter 1960, when age at FFTP was again

on the rise.

Brian E. Henderson
Ronald K. Ross
Mimi C. Yu
Leslie Bernstein

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Re: Prospective Study of Sex Hormone Levels and Risk of Prostate Cancer

Gann et al. (1) reported that testosterone and sex hormone-binding globulin (SHBG) are independent and opposing risk factors for prostate cancer, while low circulating estradiol could be an additional risk factor. Their study has several advantages over those previously reported, in particular, measurement of hormones before cancer diagnosis and a much larger sample size [reviewed in (2)].

We have recently reported a population-based case-control study encompassing 93 patients with newly diagnosed, untreated prostate cancer and 98 control subjects. We found no clear association between testosterone, estradiol, and SHBG on the one hand and the risk of prostate cancer on the other (2). However, we evaluated each hormone without taking into consideration the possible mutual confounding effects—revealed subsequently in the study by Gann et al. (1)—that prompted us to reanalyze our data.

We found that the correlations between total testosterone and SHBG (Spearman \( r = .55 \)) and between total testosterone and estradiol (\( r = .29 \)) were virtually identical with those reported by Gann et al. (1) for their prospectively collected blood. Moreover, in our data, free testosterone (not analyzed in the study by Gann et al.) was also correlated with estradiol (\( r = .30 \)), but only weakly with SHBG (\( r = .13 \)). We further tried to disentangle possible independent effects of testosterone, estradiol, and SHBG by mutual adjustment; for comparison we also show data without such adjustment (Table 1).

Associations between mutually adjusted testosterone and SHBG and risk for prostate cancer are weaker than in the study by Gann et al., and the confidence intervals are wide. The risk estimates from univariate analyses of estradiol and SHBG and prostate cancer in our study did not appear to be confounded by testosterone, since odds ratios and \( P \) values for trend are largely unaffected by mutual adjustment.

In agreement with the results of Gann et al., effects of testosterone and estradiol on prostate cancer seem to be more pronounced in older men. In our study, the weaker effect of SHBG could be due to the fact that our study subjects were 8 years older on average (mean age, 70 years versus 62 years in the study by Gann et al.); in fact, our estimates for SHBG are compatible with their estimates in the subgroup of men 62 years of age and older.

It appears that patterns in associations of testosterone, estradiol, and SHBG with prostate cancer in our case-control study are in general compatible with those observed by Gann et al. in their prospective investigation and point to a complex but biologically meaningful interplay of hormones in the etiology of prostate cancer.

Table 1. Risk for prostate cancer by tertile of plasma level of total testosterone (T), free testosterone (TF), estradiol (E2), and sex hormone-binding globulin (SHBG)*

<table>
<thead>
<tr>
<th>Hormones adjusted for</th>
<th>OR by tertile</th>
<th>95% CI for 3rd tertile</th>
<th>( P ) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total testosterone (T), ng/mg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;3.50)</td>
<td>3.50-5.07</td>
<td>&gt;5.07</td>
<td>0.49-1.94</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.0</td>
<td>1.18</td>
<td>0.97</td>
</tr>
<tr>
<td>Age, E2, and SHBG</td>
<td>1.0</td>
<td>1.23</td>
<td>1.27</td>
</tr>
<tr>
<td>Age, E2, and SHBG (men ≥70 y)</td>
<td>1.0</td>
<td>2.28</td>
<td>1.81</td>
</tr>
<tr>
<td>TF, pg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;70.0)</td>
<td>70.0-94.2</td>
<td>&gt;94.2</td>
<td>0.60-2.42</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.0</td>
<td>1.51</td>
<td>1.51</td>
</tr>
<tr>
<td>Age, E2, and SHBG</td>
<td>1.0</td>
<td>1.51</td>
<td>1.46</td>
</tr>
<tr>
<td>Age, E2, and SHBG (men ≥70 y)</td>
<td>1.0</td>
<td>1.40</td>
<td>1.71</td>
</tr>
<tr>
<td>E2, pg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;11.6)</td>
<td>11.6-23.0</td>
<td>&gt;23.0</td>
<td>0.31-1.25</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.0</td>
<td>0.85</td>
<td>0.62</td>
</tr>
<tr>
<td>Age, TF, and SHBG</td>
<td>1.0</td>
<td>0.84</td>
<td>0.60</td>
</tr>
<tr>
<td>Age, TF, and SHBG (men ≥70 y)</td>
<td>1.0</td>
<td>0.59</td>
<td>0.49</td>
</tr>
<tr>
<td>SHBG, nmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;40.3)</td>
<td>40.3-59.7</td>
<td>&gt;59.7</td>
<td>0.37-1.56</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.0</td>
<td>0.90</td>
<td>0.76</td>
</tr>
<tr>
<td>Age, T, and E2</td>
<td>1.0</td>
<td>0.84</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Odds ratios (ORs), with 95% confidence intervals (CIs) for the highest compared with the lowest tertile, obtained through logistic regression.

References


Notes

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